Clinical Analysis of Adverse Drug Reactions

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Objectives

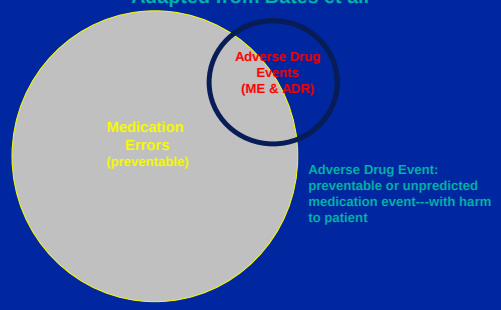
- Define adverse drug reactions
- Discuss epidemiology and classification of ADRs
- Describe basic methods to detect, evaluate, and document ADRs

Definition

- WHO
  - response to a drug that is *noxious and unintended* and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function
  - excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

Adverse Drug Events

Adapted from Bates et al.



Epidemiology of ADRs

- substantial morbidity and mortality
- estimates of incidence vary with study methods, population, and ADR definition
- 4th to 6th leading cause of death among hospitalized patients*
- 6.7% incidence of serious ADRs*
- 0.3% to 7% of all hospital admissions
- annual dollar costs in the billions
- 30% to 60% are preventable

*JAMA. 1998;279:1200-1205.

Classification

- Onset
- Severity
- Type

Classification

- Onset of event:
  - Acute
    - » within 60 minutes
  - Sub-acute
    - » 1 to 24 hours
  - Latent
    - » > 2 days

Classification - Severity

- Severity of reaction:
  - Mild
    - » bothersome but requires no change in therapy
  - Moderate
    - » requires change in therapy, additional treatment, hospitalization
  - Severe
    - » disabling or life-threatening

Classification - Severity

- FDA Serious ADR
  - Result in death
  - Life-threatening
  - Require hospitalization
  - Prolong hospitalization
  - Cause disability
  - Cause congenital anomalies
  - Require intervention to prevent permanent injury

Classification

- Type A
  - » extension of pharmacologic effect
  - » often predictable and dose dependent
  - » responsible for at least two-thirds of ADRs
  - » e.g., propranolol and heart block, anticholinergics and dry mouth

Classification

- Type B
  - » idiosyncratic or immunologic reactions
  - » rare and unpredictable
  - » e.g., chloramphenicol and aplastic anemia

Classification

- Type C
  - » associated with long-term use
  - » involves dose accumulation
  - » e.g., phenacetin and interstitial nephritis or antimalarials and ocular toxicity

Classification

- Type D
  - » delayed effects (dose independent)
  - » Carcinogenicity (e.g., immunosuppressants)
  - » Teratogenicity (e.g., fetal hydantoin syndrome)

Classification

– Types of allergic reactions
- Type I - immediate, anaphylactic (IgE)
  - » e.g., anaphylaxis with penicillins
- Type II - cytotoxic antibody (IgG, IgM)
  - » e.g., methyldopa and hemolytic anemia
- Type III - serum sickness (IgG, IgM)
  - » antigen-antibody complex
  - » e.g., procainamide-induced lupus
- Type IV - delayed hypersensitivity (T cell)
  - » e.g., contact dermatitis

Classification - Type

Reportable

- All significant or unusual adverse drug reactions as well as unanticipated or novel events that are suspected to be drug related

Classification - Type

Reportable

- Hypersensitivity
- Life-threatening
- Cause disability
- Idiosyncratic
- Secondary to Drug interactions
- Unexpected detrimental effect
- Drug intolerance
- Any ADR with investigational drug

Common Causes of ADRs

- Antibiotics
- Antineoplastics*
- Anticoagulants
- Cardiovascular drugs*
- Hypoglycemics
- Antihypertensives
- NSAID/Analgesics
- Diagnostic agents
- CNS drugs*

*account for 69% of fatal ADRs

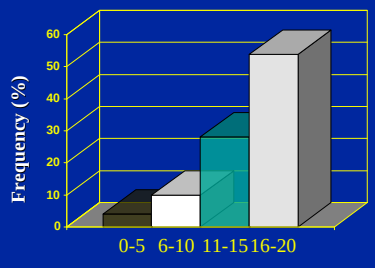
Body Systems Commonly Involved

- Hematologic
- CNS
- Dermatologic/Allergic
- Metabolic
- Cardiovascular
- Gastrointestinal
- Renal/Genitourinary
- Respiratory
- Sensory

ADR Risk Factors

- Age (children and elderly)
- Multiple medications
- Multiple co-morbid conditions
- Inappropriate medication prescribing, use, or monitoring
- End-organ dysfunction
- Altered physiology
- Prior history of ADRs
- Extent (dose) and duration of exposure
- Genetic predisposition

ADR Frequency by Drug Use



May FE. Clin Pharmacol Ther 1977;22:322-8

ADR Detection

- Subjective report
  - patient complaint
- Objective report:
  - direct observation of event
  - abnormal findings
    - » physical exam
    - » laboratory test
    - » diagnostic procedure

ADR Detection

- Medication order screening
  - abrupt medication discontinuation
  - abrupt dosage reduction
  - orders for “tracer” or “trigger” substances
  - orders for special tests or serum drug concentrations
- Spontaneous reporting
- Medication utilization review
  - Computerized screening
  - Chart review and concurrent audits

ADR Detection in Clinical Trials

- Methods
  - Standard laboratory tests
  - Diagnostic tests
  - Complete history and physical
  - Adverse drug event questionnaire
    - » Extensive checklist of symptoms categorized by body system
    - » Review-of-systems approach
    - » Qualitative and quantitative

ADR Detection in Clinical Trials

Limitations

- exposure limited to few individuals
  - » rare and unusual ADRs not detected
  - » 3000 patients at risk are needed to detect ADR with incidence of 1/1000 with 95% certainty
- exposure is often short-term
  - » latent ADRs missed
- external validity
  - » may exclude children, elderly, women of child-bearing age; and patients with severe form of disease, multiple co-morbidities, and those taking multiple medications

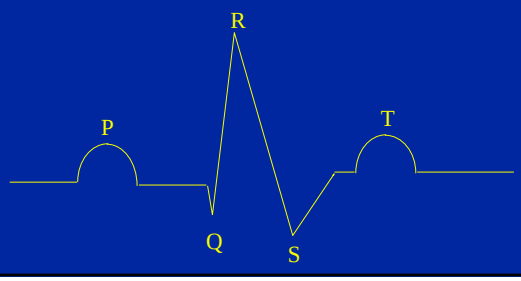
Preliminary Assessment

- Preliminary description of event:
  - Who, what, when, where, how?
  - *Who* is involved?
  - *What* is the most likely causative agent?
    - Is this an exacerbation of a pre-existing condition?
    - Alternative explanations / differential diagnosis
  - *When* did the event take place?
  - *Where* did the event occur?
  - *How* has the event been managed thus far?

Preliminary Assessment

- Determination of urgency:
  - What is the patient's current clinical status?
  - How severe is the reaction?
- Appropriate triage:
  - Acute (ER, ICU, Poison Control)

Detailed Description of Event PQRSTA Acronym



Detailed Description of Event

- History of present illness
- Signs / Symptoms: PQRSTA
  - Provoking or palliative factors
  - Quality (character or intensity)
  - Response to treatment, Radiation, Reports in literature
  - Severity / extent, Site (location)
  - Temporal relationship (onset, duration, frequency)
  - Associated signs and symptoms

Pertinent Patient/Disease Factors

- Demographics
  - age, race, ethnicity, gender, height, weight
- Medical history and physical exam
  - Concurrent conditions or special circumstances
    - e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding
  - Recent procedures or surgeries and any resultant complications
    - e.g., contrast material, radiation treatment, hypotension, shock, renal insufficiency

Pertinent Patient/Disease Factors

- End-organ function
- Review of systems
- Laboratory tests and diagnostics
- Social history
  - tobacco, alcohol, substance abuse, physical activity, environmental or occupational hazards or exposures
- Pertinent family history
- Nutritional status
  - special diets, malnutrition, weight loss

Pertinent Medication Factors

- Medication history
  - Prescription medications
  - Non-prescription medications
  - Alternative and investigational therapies
  - Medication use within previous 6 months
  - Allergies or intolerances
  - History of medication reactions
  - Adherence to prescribed regimens
  - Cumulative mediation dosages

Pertinent Medication Factors

- Medication
  - Indication, dose, diluent, volume
- Administration
  - Route, method, site, schedule, rate, duration
- Formulation
  - Pharmaceutical excipients
    - » e.g., colorings, flavorings, preservatives
  - Other components
    - » e.g., DEHP, latex

Pertinent Medication Factors

- Pharmacology
- Pharmacokinetics (LADME)
- Pharmacodynamics
- Adverse effect profiles
- Interactions
  - drug-drug
  - drug-nutrient
  - drug-lab test interference
- Cross-allergenicity or cross-reactivity

ADR Information

- Incidence and prevalence
- Mechanism and pathogenesis
- Clinical presentation and diagnosis
- Time course
- Dose relationship
- Reversibility
- Cross-reactivity/Cross-allergenicity
- Treatment and prognosis

ADR Information Resources

- Tertiary
  - »Reference books
    - – Medical and pharmacotherapy textbooks
    - – Package inserts, PDR, AHFS, USPDI
    - – Specialized ADR resources
      - Meyler's Side Effects of Drugs
      - Textbook of Adverse Drug Reactions
    - – Drug interactions resources
    - – Micromedex databases (e.g., TOMES, POISINDEX, DRUGDEX)
  - »Review articles

ADR Information Resources

- Secondary
  - »MEDLARS databases (e.g., Medline, Toxline, Cancerline, Toxnet)
  - »Excerpta Medica's Embase
  - »International Pharmaceutical Abstracts
  - »Current Contents
  - »Biological Abstracts (Biosis)
  - »Science Citation Index
  - »Clin-Alert and Reactions

ADR Information Resources

- Primary
  - » Spontaneous reports or unpublished data
    - – FDA
    - – Manufacturer
  - » Anecdotal and descriptive reports
    - – Case reports, case series
  - » Observational studies
    - – Case-control, cross-sectional, cohort
  - » Experimental and other studies
    - – Clinical trials
    - – Meta-analyses

Causality Assessment

- Prior reports of reaction
- Temporal relationship
- De-challenge
- Re-challenge
- Dose-response relationship
- Alternative etiologies
- Objective confirmation
- Past history of reaction to same or similar medication

Causality Assessment

– Examples of causality algorithms
- Kramer
- Naranjo and Jones

– Causality outcomes
- Highly probable
- Probable
- Possible
- Doubtful

Naranjo ADR Probability Scale

Naranjo CA. Clin Pharmacol Ther 1981;30:239-45

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

		Yes	No	Do Not Know	Score
1.	Are there previous *conclusive* reports on this reaction?	+1	0	0	___
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	___
3.	Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	___
4.	Did the adverse reactions appear when the drug was readministered?	+2	-1	0	___
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	___
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	___
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	___
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	___
9.	Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	___
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	___
				Total Score	___

Total Score	*ADR Probability Classification*
9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

Management Options

- **Discontinue the offending agent if:**
  - **it can be safely stopped**
  - **the event is life-threatening or intolerable**
  - **there is a reasonable alternative**
  - **continuing the medication will further exacerbate the patient's condition**
- **Continue the medication (modified as needed) if:**
  - **it is medically necessary**
  - **there is no reasonable alternative**
  - **the problem is mild and will resolve with time**

Management Options

- **Discontinue non-essential medications**
- **Administer appropriate treatment**
  - **e.g., atropine, benztropine, dextrose, antihistamines, epinephrine, naloxone, phenytoin, phytonadione, protamine, sodium polystyrene sulfonate, digibind, flumazenil, corticosteroids, glucagon**
- **Provide supportive or palliative care**
  - **e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics**
- **Consider rechallenge or desensitization**

Follow-up and Re-evaluation

- Patient's progress
- Course of event
- Delayed reactions
- Response to treatment
- Specific monitoring parameters

Documentation and Reporting

- Medical record
  - Description
  - Management
  - Outcome
- Reporting responsibility
  - JCAHO-mandated reporting programs
  - Food and Drug Administration
    - » post-marketing surveillance
    - » particular interest in serious reactions involving new chemical entities
  - Pharmaceutical manufacturers
  - Publishing in the medical literature

Components of an ADR Report

- Product name and manufacturer
- Patient demographics
- Description of adverse event and outcome
- Date of onset
- Drug start and stop dates/times
- Dose, frequency, and method
- Relevant lab test results or other objective evidence
- De-challenge and re-challenge information
- Confounding variables

MEDWATCH 3500A
Reporting
Form

https://www.accessdata.fda.gov/scripts/medwatch